REMARKS

Claims 7-9, 12-13, 18-20, 22 and 33 were pending in the application. Claims 25-33 have been withdrawn from further consideration, claims 7-9, 12-13, 18-20 and 22 have been amended, and claim 40 is new. Therefore, upon entry of this paper, claims 7-9, 12-13, 18-20, 22, 33 and 40 will be pending.

Claims 7 and 18 have been amended to exclude restricted subject matter. Claims 7-9, 12-13, 18-20 and 22 have been amended to clarify the invention.

Support for the amendments to claims 7-9, 12-13, 18-20 and 22 for the variables R_1, R_2, R_6, R_8 and R_9 can be found, at least, in originally filed claims 7-9, 12-13, 18-20 and 22 and in the Examples, in particular, Example 11, found on page 50, through Example 31-7, found on page 82, Examples 42, found on page 92, through Examples 44, found on page 93, and Examples 46, found on page 95, through Examples 49, found on page 106, of the originally filed specification. Support for the amendment to claim 7 for the variable Z can be found, at least, in originally filed claim 1 from which claims 7 was dependent. Support for new claim 40 can be found, at least, in originally filed claim 33.

The foregoing claim amendments should in no way be construed as acquiescence to any of the Examiner's objections and/or rejection, and have been made solely to expedite prosecution of the present application. Applicants reserve the option to further prosecute the same or similar claims in the present or another patent application. No new matter has been added.

Applicants thank the Examiner for the interview granted on April 6, 2009 and note with appreciation the Examiner's withdrawal of the rejection of claims 18, 19, 20 and 33 under 35 USC § 103. Applicants also thank the Examiner for his time on the phone October 15, 2009.

Restriction Requirement

The Examiner has indicated that the claims have not been restricted to the elected group I, *i.e.* the instant claims have not been restricted to compounds and pharmaceutical compositions of Formulas Ia, Ih and Ii wherein X and Y are carbon (phenyl and naphthyl) with no additional ring fusing and wherein R_3 and R_4 form a hydroquinoline. Applicants have amended claims 7 and 18 to comply with the restriction requirement, as requested by the Examiner.

Rejection of Claims 7-9, 12-13, 18-20, 22 and 33 under 35 U.S.C. §112, first paragraph

Claims 7-9, 12-13, 18-20, 22 and 33 stand rejected under 35 U.S.C. §112 first paragraph because the Examiner believes they are not enabled for the full scope of the defined markush groups of R_1 and R_2 and R_6-R_9. Applicants respectfully traverse this assertion. However, *solely in the interest of expediting prosecution,* Applicants have amended the instantly claimed compounds to conform with the Examiner's suggestion for enabled subject matter.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. §112 rejection.

Rejection of Claims 7, 8 and 33 under 35 U.S.C. §102(b)

Claims 7, 8 and 33 stand rejected under 35 U.S.C. §102(b) as being anticipated by Ogawa '113 (WO 94/01113A1). Applicants respectfully traverse.

Ogawa '113 discloses hundreds of compounds but only discloses one perhydroquinoline derivative (compound 2-149, at page 146, which was cited by the Examiner), *i.e.* the group corresponding to R_6 in the instant application is phenyl substituted with an alkyl.

In contrast, Applicants respectfully submit that instantly claimed variable R_6 is an optionally substituted C_{1-4} alkyl, *phenyl*, naphthyl, thienyl, furanyl, pyrrolyl, morpholinyl, piperidinyl, piperazinyl, pyridinyl, benzothiophenyl, benzodioxoyl or cycloalkyl optionally substituted by one to four substituents such as halo, hydroxy, alkoxy, alkanoyl, alkanoyloxy, optionally substitued amino, thiol, alkylthio, nitro, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, alkylthiono, arylsulfonyl, sulfonamido and heterocycloyl.

Accordingly, the compounds exemplified in Ogawa '113 do not anticipate the amended claim scope because Ogawa *et al.*, only discloses a compound in which the position corresponding to instatly claim variable R_6 is a phenyl substituted with an alkyl.

Therefore, Applicants respectfully request reconsideration and withdrawal of this rejection of claims 7, 8 and 33 under 35 U.S.C. §102(b).

Claim Objections

The Examiner's objection to claim 18, and its dependent claims, has been rendered moot by the amendment of claim 18 into independent format.

Rejection of Claims 7, 8, 9 and 33 Under 35 U.S.C. §103(a)

Claims 7, 8, 9 and 33 stand rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Ogawa *et al.* In particular, the Examiner is of the opinion that "[i]t would obvious for one of ordinary skill to try to make compounds of Formula Ia...with reasonable expectation of success from the disclosed compounds and teachings of Ogawa *et al.*, and that "[a] hydrogen and methyl are obvious variants." Applicants respectfully disagree for at least the following reasons.

The compounds of the invention are inhibitors of 11β-hydroxysteroid dehydrogenase type 1 reductase activity, and are discussed above. In comparison, the compounds of Ogawa et al. are oxytocin agonists, in particular compound 2-149, discussed above.

From the outset, Applicants note that Ogawa *et al.* fails to teach or suggest the compounds in the genus of claim 7, and further fails to teach or suggest the specific compounds set forth in claims 8 and 9, and fails to teach or suggest the pharmaceutical compositions of

claim 33. Moreover, the compounds of Ogawa *et al.*, are limited to oxytocin agonists, whereas, the instantly claimed compounds are directed to 11β-hydroxysteroid dehydrogenase type 1 reductase activity.

As the Federal Circuit set forth in *Takeda Chem. Indust. V. Alphapharm Pty., Ltd.*, (attached herewith as Appendix A and hereinafter "*Takeda*"), the case law concerning *prima facie* obviousness of structurally similar compounds is well settled.[1] Specifically, the Court, citing *In re Dillon*, states that "structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness."[2] However, the court in *Takeda* goes on to clarify this finding by stating that in order to find a prima facie case of unpatentability in cases of structurally similar compounds, ***"a showing that the 'prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention' was also required."***[3] The *Takeda* court further states that "***in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner*** to establish prima facie obviousness of a new claimed compound."[4]

The facts of *Takeda* are analogous to the present case. In *Takeda*, Alphapharm had identified a prior art compound ("compound b"), which it asserted was the compound in the prior art that would have been most promising to modify in order to improve upon its beneficial properties. Alphapharm further asserted that upon selection of this specific compound, it would have been obvious to one of skill in the art to, among other modifications, replace a methyl group with an ethyl group (*i.e.*, homologation).[4] However, the Federal Circuit in *Takeda* refused to find that the claims of the disputed patent were obvious in view of either "compound b" or "homologation."[5]

Specifically, with respect to selecting compound b for further modification in *Takeda*, the Federal Circuit found that the cited prior art disclosed a plethora of compounds, including compound b, and that although the prosecution history disclosed test results of compound b and eight other compounds, there was nothing in the prior art patent to suggest to one of skill in the art to select compound b out of the tremendous number of compounds covered by the patent as the best performing compound, and thus, target it for further modification to obtain improved properties.[6]

Similarly, in the present case, the Examiner has selected the compound 2-149 of Ogawa *et al.* as a compound that one of skill in the art would modify to arrive at the currently claimed

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[1] *Takeda Chem. Indust. v. Alphapharm Pty., Ltd.* 492 F.3d 1350 (Fed. Cir. 2007).
[2] *Id.* at 1356.
[3] *Id.* at 1356 (emphasis added), citing *In re Jones*, 958 F.2d 347 (Fed. Cir. 1992); *In re Dillon* 919 F.2d 688 (Fed. Cir. 1992); *In re Grabiak*, 769 F.2d 729 (Fed. Cir. 1985) and *In re Lalu* 747 F.2d 703 (Fed. Cir. 1984).
[4] *Id* at 1357 (emphasis added).
[5] *Id.* at 1362-3.
[6] *Id.* at 1358.

compounds. However, Applicants note that as in the prior art cited by Alphapharm in *Takeda*, ***Ogawa et al. disclose a very large numbers of chemical compounds***. Thus, selection of compound 2-149 of Ogawa *et al.* for modification can only be based on hindsight using applicants' disclosure.

Moreover, even if compound 2-149 of Ogawa *et al.* was selected for modification, Ogawa *et al.* also ***fails to identify any reason that would lead a chemist to modify compound 2-149*** because there are no finite number of predictable solutions which would lead the skilled artisan from the Oxytocin antagonist of Ogawa *et al.* to the Applicants' particular 11β-hydroxysteroid dehydrogenase type 1 antagonist.

The *Takeda* court addressed the issue of "obvious to try" with respect to homologation. Specifically, in *Takeda*, Alphapharm asserted that using the technique of homologation would have been "obvious to try." However, the *Takeda* court disagreed. In particular, the Court stated that "rather than identify predictable solutions...the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation" and that "this case fails to present the type of situation contemplated by the court when it stated that an invention may be deemed obvious if it was 'obvious to try.'"[7] Finally, the *Takeda* court also specifically addressed Amphapharm's allegations that "homologation" would have been obvious to one of skill in the art. In particular, the Federal Circuit found nothing in the prior art "to suggest to one of ordinary skill in the art that homologation would bring about a reasonable expectation of success."[8]

Thus, there is nothing in Ogawa *et al.* to suggest to one of skill in the art to select the compound 2-149, much less any compound disclosed in Ogawa *et al.*, out of the tremendous number of compounds covered by Ogawa *et al.*, or to modify the compounds to arrive at the Applicants compounds.

Comparable to *Takeda*, in the instant application, Ogawa *et al.* discloses a broad number of compounds without identifying any predictable solutions to enhance the activity, efficacy or safety of such compounds, and any one of the broad number of compounds disclosed in these patents could have been selected for further modification. Moreover, as described above, Ogawa *et al.* fails to provide any suggestion or motivation to select any compound disclosed within this publication for further modification, nor does this publication contain a suggestion or motivation for achieving "predictable results" when modifying the disclosed compounds.

In view of the foregoing, Applicants submit that claims 7-9 and 33 are patentable over Ogawa *et al.* because this publication fails to provide motivation for selecting compound 2-149 as lead compound for modification. Ogawa *et al.* also fails to provide a reasonable expectation of success for modification of the compound 2-149, as described above. Moreover, Applicants respectfully submit that Ogawa *et al.* fails to provide any motivation for arriving at the specific

[7] *Id.* at 1359.
[8] *Id.* at 1361.

compounds and pharmaceutical compositions comprising such specific compounds. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

Conclusion

Applicants have addressed each and every issue set forth by the Examiner. Applicants respectfully submit that the present application is in good condition for allowance. Applicants have not amended the claims to cause the Examiner to perform additional searching and respectfully request consideration and withdrawal of the outstanding rejection and enter a Notice of Allowance.

If the Examiner believes for any reason that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (617) 871-7802.

If necessary, the Commissioner is hereby authorized in this, concurrent, and further replies, to charge payment or credit any overpayment to Deposit Account No. 50-4409 for any additional fees under 37 C.F.R. §1.16 or under 37 C.F.R. §1.17; particularly extension of time fees.

Respectfully submitted,

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